AMENDMENTS TO THE DRAWINGS

The replacement sheets of drawings include changes to Figures 1, 5 and 6. As a courtesy, all four replacement sheets are submitted herewith.

Attachment: Replacement sheets (4 sheets, 7 figures)

REMARKS

Status of the Claims

Claims 1 and 3-8 were presented for examination and were rejected. With this amendment, claims 1, 3 and 8 are amended to clarify the invention, and new claims 9-20 are added. Support for the amendment and the new claims may be found throughout the application as filed, for example, at paragraphs **[0005]**, **[0014]** and **[0015]**, in Figures 1-6, and in the original claims. Thus, no new matter has been added. Upon entry of this amendment, claims 1 and 3-20 will be pending. Entry of the amendment and reconsideration in view of the following comments is respectfully requested.

With respect to all amendments, Applicants have not dedicated or abandoned any unclaimed subject matter and moreover have not acquiesced to any rejections and/or objections made by the Patent Office. Applicants expressly reserve the right to pursue prosecution of any presently excluded subject matter or claim embodiments in one or more future continuation and/or divisional application(s).

Amendments to the Drawings

While reviewing the application, the undersigned noticed several errors and omissions in the drawings. Specifically, Figure 1 was missing the letter identifiers of the longitudinal view referred to in paragraphs **[0011]** and **[0014]** of the application as filed, Figure 5 was erroneously labeled as "Figure 6", and Figure 6 was erroneously labeled as "Figure 5". Replacement drawings are submitted herewith to correct these errors and omissions.

Figure 1 now contains the A-A directional identifiers, and the labels for Figures 5 and 6 are switched to bring these figures into conformance with the written description. Per 37 CFR 1.84(c), the replacement drawings are labeled "Replacement Sheet" in the page headers. No new matter has been added. Favorable consideration of the enclosed drawings and replacement of the previously submitted drawings with the enclosed drawings are respectfully requested.

Rejection under 35 U.S.C. § 102

Claims 1, 3 and 6-8 stand rejected under 35 U.S.C. § 102(e) as allegedly being anticipated by Zhao *et al.* (US 6,939,451, hereinafter "Zhao").

The Office essentially reiterates its earlier argument that Zhao discloses a capillary electrophoresis chip apparatus comprising an electrophoresis chip having an upper planar substrate with one or more microchannels and one or more apertures for loading samples; a middle electrode layer that bonds to the bottom of the substrate enclosing and sealing the microchannels to form an intact capillary and providing the voltage for electrophoresis; and a lower heating layer wherein the individual layers are thermally conductive and adhesive to each other. (The OA at pages 2-4). The Office cites to a number of passages in Zhao that allegedly teach a two-dimensional or multi-dimensional microchannel and multiple heating elements capable of establishing a stable temperature gradient. (*Id.*) The Office takes the position that the electrophoretic chip of Zhao is inherently capable of detecting a nucleotide polymorphism or a single polymorphism because it possesses all the requisite structural elements. (The OA at page 9).

Applicants respectfully traverse this rejection for the reasons of record and for the additional reasons set forth below.

The legal standard for anticipation under 35 U.S.C. § 102 is one of strict identity. *Trintec Industries, Inc. v. Top-U.S.A. Corp.*, 63 U.S.P.Q.2d 1597 (Fed. Cir. 2002). To anticipate a claim, a single prior source must contain each and every limitation of the claimed invention. *In re Paulson*, 30 F.3d 1475, 1478-79, 31 USPQ2d 1671, 1673 (Fed. Cir. 1994) (*citing In re Spada*, 911 F.2d 705, 708, 15 USPQ2 d 1655, 1657 (Fed. Cir. 1990)). "A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987); MPEP § 2131.

As an initial matter, claim 1 has been amended to read as follows:

> A capillary electrophoresis chip apparatus for detecting a nucleotide polymorphism or a single nucleotide polymorphism, said apparatus comprising an electrophoresis chip comprising:
>
> an upper channel layer, comprising a first-dimension microfluidic channel, a plurality of second-dimension microfluidic channels in fluid communication with the first-dimension microfluidic channel, and two or more sets of electrode apertures in fluid communication with the first-dimension microfluidic channel and with the plurality of second-dimension microfluidic channels;
>
> a middle electrode layer capable of sealing the first-dimension microfluidic channel and the plurality of second-dimension microfluidic channels to form intact capillaries, said middle electrode layer comprising electrodes capable of providing a needed voltage along the first-dimension microfluidic channel and along the plurality of second-dimension microfluidic channels; and
>
> a lower heating layer capable of providing a stable temperature gradient for electrophoresis along the plurality of second-dimension microfluidic channels, said lower heating layer comprising two or more sets of temperature control elements that are spaced apart from each other and positioned approximately perpendicular to the plurality of second-dimension microfluidic channels,
>
> wherein the upper channel layer, the middle electrode layer, and the lower heating layer are thermally conductive and adhesive to each other, and the capillary electrophoresis chip apparatus is capable of detecting a nucleotide polymorphism or a single nucleotide polymorphism.

The key inventive feature of the present invention is the combination of two-dimensional electrophoresis using multiple second-dimension microchannels with a stable thermal gradient along the second-dimension microchannels. It is this combination that provides for a high resolution of nucleic acids and permits detection of single-nucleotide mismatches, as explained in paragraph **[0015]** and Figure 7 of the present application as filed. Thus, in order to anticipate the present invention, a prior art reference must teach, *inter alia*, (1) an upper layer having a plurality of second-dimension microfluidic channels in fluid communication with a first-dimension microfluidic channel; (2) a middle layer having electrodes capable of providing an electric driving force along the plurality of second-dimension microfluidic channels; and (3) a lower layer having two or more sets of temperature control elements spaced apart from each other and positioned approximately perpendicular to the plurality of second-dimension microfluidic channels that are capable of providing a stable thermal gradient along the plurality of second-dimension microfluidic channels.

Applicants respectfully submit that Zhao does not teach these elements.

The Office alleges that Zhao teaches "an upper layer (18), comprising a two-dimensional or multidimensional microfluidic channel (14) (Fig. 1; Col. 5, lines 55-57; Col. 6, lines 24-25; Col. 15, lines 57-60; also US 5,599,432 incorporated by reference)" (the OA at page 3).

Figures 1 and 2 of Zhao are shown below.

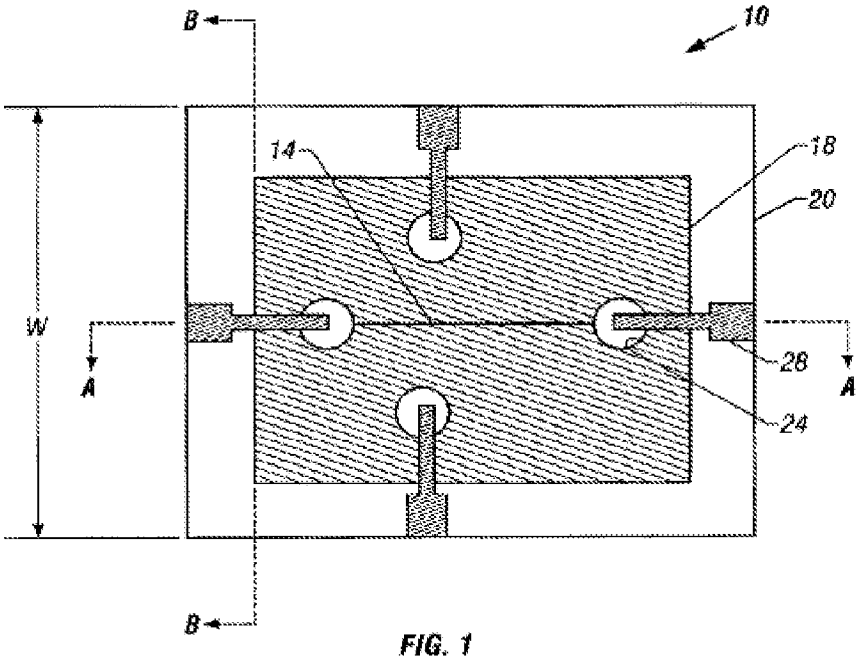

FIG. 1

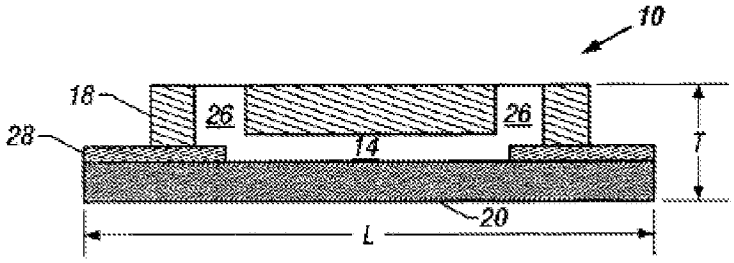

FIG. 2

Col. 5, lines 55-57 of Zhao states:

> The substrate **18** typically features at least one generally planar surface having one or more microchannels **14** and one or more apertures or through-holes **24** in fluid communication with the microchannels. (Emphasis added).

Col. 6, lines 24-25 of Zhao states:

> While not shown, the cover may also include one or more microchannels and apertures. (Emphasis added).

Col. 15, lines 57-60 of Zhao states:

> The devices were put together as follows: an ink electrode was screen printed on the polymer film first and then laminated to a substrate having channels and reservoirs. Alignment during the lamination assures the ink electrodes were placed in the reservoirs as indicated in FIG. 1. (Emphasis added).

None of the cited passages of Zhao teaches a plurality of second-dimension microfluidic channels in fluid communication with a first-dimension microfluidic channel, as recited in the present claim 1 as amended. All that can be inferred from these passages is that the electrophoretic chip of Zhao may have one or more microchannels and one or more apertures in fluid communication with the microchannels. However, no particular arrangement of the microchannels is disclosed. As Applicants have previously submitted, Figure 1 of Zhao shows only one horizontal microchannel **14**. The Office's argument that a second, vertical microchannel could be made by connecting the unconnected apertures in Figure 1 does not constitute a teaching, express or implicit. Figure 5 of Zhao teaches that electrodes perpendicular to the microchannel (**503**) do not necessarily have to be connected by a microchannel and may serve, for example, as an electrochemical detector (**501**) instead (see below). Even if we assume, *arguendo*, that Figure 1 of Zhao does teach a vertical microchannel perpendicular to microchannel **14**, it does not teach a plurality of second-dimension microfluidic channels, which is a critically important feature for the practice of the present invention.

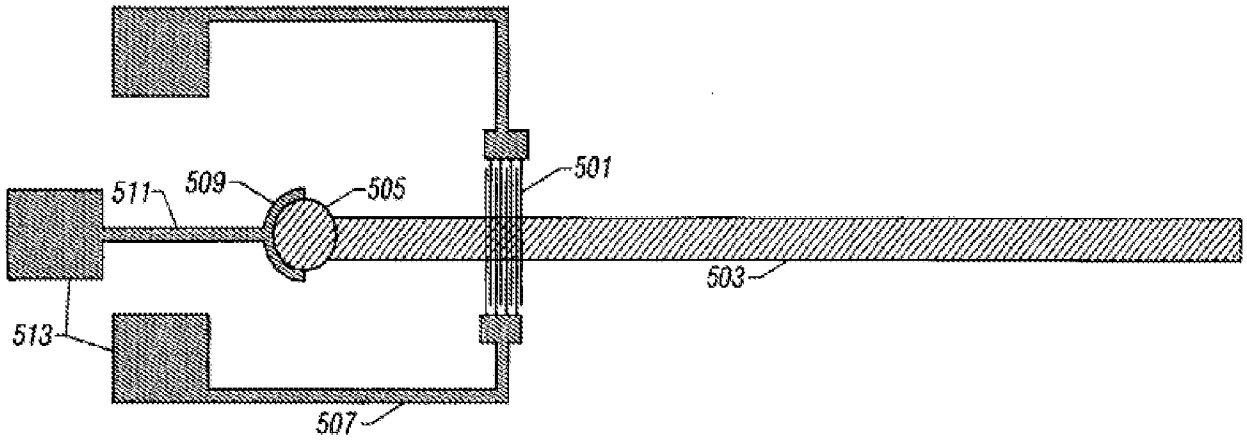

FIG. 5

US 5,599,432 is also cited by the Office in support of the proposition that Zhao teaches an upper layer comprising a two-dimensional or multidimensional microfluidic channel. However, a careful review of this reference reveals that it actually teaches away from the presently claimed electrophoretic chip apparatus:

> Coupling a large number of separating capillaries next to one another to achieve "two dimensionality" in order thus to be able also to separate highly complex substance mixtures would, however, require in the case of miniaturised systems connection pieces of subnanolitre volumes. Such connection pieces would, however, be very difficult and expensive to manufacture, if they could be manufactured at all. With very short capillary separating paths for very rapid separations, the disturbing effect of the dead spaces of the connection pieces is particularly high. Those dead spaces would therefore have to be kept vanishingly small, which appears to be impossible in practice. The construction of the separating path of a miniaturised capillary electrophoresis system as a flat bed, analogously to 2D gel electrophoresis, would promote the diffusion of the separated components and thus result in a marked impairment of the separating performance. (US 5,599,432 at col. 4, lines 1-17, emphasis added).

In view of the foregoing discussion, it is apparent that Zhao does not teach a plurality of second-dimension microfluidic channels in fluid communication with a first-dimension microfluidic channel, as recited in the present claim 1 as amended.

The Office further alleges that Zhao teaches "a middle electrode layer comprising electrodes (capable of providing a needed voltage for the electrophoresis chip) (Col. 5, 55-64; Col. 12, 28-34)" (the OA at page 3).

Col. 5, lines 55-64 of Zhao states:

> The substrate **18** typically features at least one generally planar surface having one or more microchannels **14** and one or more apertures or through-holes **24** in fluid communication with the microchannels. Wells or reservoirs **26** are formed at the through-holes **24** when the cover **20** is bonded to the substrate **18** as shown in FIGS. **1** and **2**. In one variation, a thin film cover is bonded to the bottom of the substrate thereby enclosing and sealing the microchannels. Access to the channels is provided via the through-holes in the substrate. (Emphasis added).

Col. 12, lines 28-34 of Zhao states:

> In a variation to this design, the components can be integrated in an independent cover lid that seals the reservoirs or sample wells of the device and minimizes evaporation. In such a configuration, the components will generally consist of driving electrodes positioned such that they will be in fluid contact with the reservoirs. (Emphasis added).

Thus, there is no evidence that Zhao teaches a middle layer having electrodes capable of providing an electric driving force along a plurality of second-dimension microfluidic channels.

The Office further alleges that Zhao teaches "a lower heating layer (301) (capable of providing a table [*sic*] temperature gradient for electrophoresis), said lower heating layer comprising two or more sets of temperature control elements that are spaced apart from each other (Fig. 7C and Col. 13, 44-49)" (the OA at page 3).

Figure 7C of Zhao is shown below:

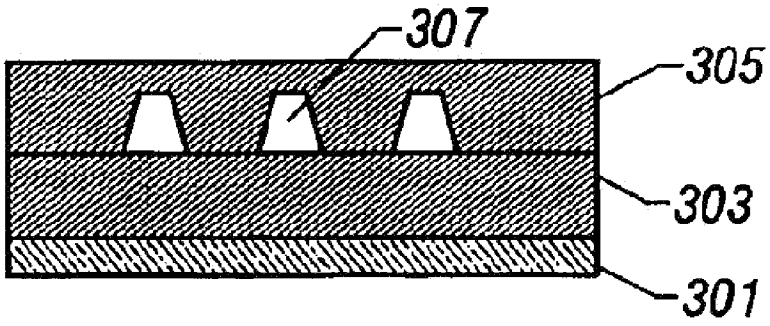

FIG. 7C

Col. 13, lines 44-49 of Zhao states:

> For purposes of controlling temperature, the components can be configured as heaters placed within certain localized regions along the channel of interest, e.g. **604**. One design for such a heater includes a serpentine-like heater element **602**, leads **606**, and contacts for the power supply **610**. (Emphasis added).

Since the cited passage refers to elements of Fig. 8, Figure 8 of Zhao is reproduced below.

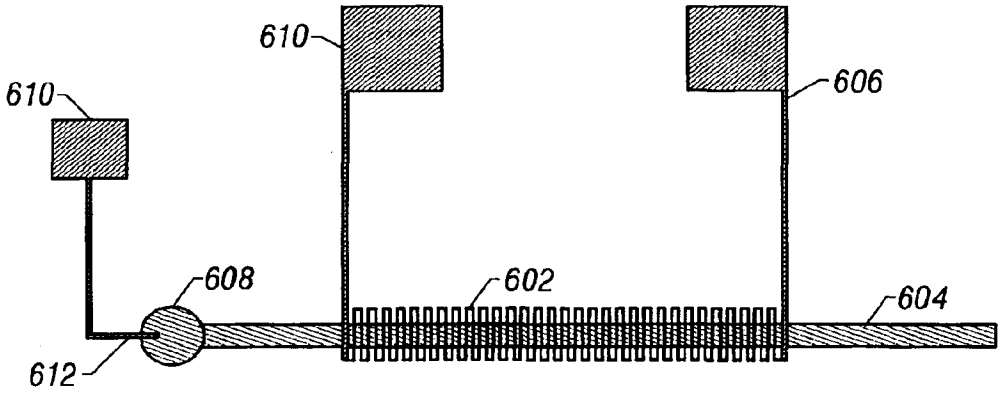

FIG. 8

Although Zhao does disclose a lower heating layer comprising heating elements positioned within localized regions along individual channels, it does not teach two or more sets of temperature control elements spaced apart from each other and positioned approximately perpendicular to a plurality of second-dimension microfluidic channels that are capable of providing a stable thermal gradient along the plurality of second-dimension microfluidic channels.

In responding to Applicants' previous arguments, the Office reiterates its position that "although it is not shown in the drawings, the upper channel layer may include one or more microchannels interconnected together which would teach a two-dimensional or multidimensional microchannel layer (Col. 15, lines 57-60; Col. 6, lines 24-25)" (the OA at page 10).

Col. 15, lines 57-60 of Zhao states:

> The devices were put together as follows: an ink electrode was screen printed on the polymer film first and then laminated to a substrate having channels and reservoirs. Alignment during the lamination assures the ink electrodes were placed in the reservoirs as indicated in FIG. 1. (Emphasis added).

Col. 6, lines 24-25 of Zhao states:

> While not shown, the cover may also include one or more microchannels and apertures. (Emphasis added).

Although the cited passages disclose one or more microchannels and apertures, they contain no teachings whatsoever of "a two-dimensional or multidimensional microchannel layer".

In summary, Applicants maintain that Zhao does not teach every limitation of claim 1 as amended. Since Zhao fails to teach every limitation of the claimed invention, the strict identity standard for anticipation is not met. Accordingly, it is respectfully submitted that this rejection under 35 U.S.C. § 102(e) may be withdrawn.

Rejections under 35 U.S.C. § 103

Zhao in View of Kaltenbach

Claims 1, 3 and 6-8 stand rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Zhao in view of Kaltenbach *et al.* (EP 0,770,871 A3, hereinafter "Kaltenbach").

The Office reiterates its position that the heating layer of Zhao would be capable of providing a stable temperature gradient. Alternatively, the Office cites Kaltenbach for its alleged teaching of a capillary electrophoresis chip comprising a miniaturized column device and a lower heating layer comprising heating elements that are in thermal contact with the middle layer and can be independently set to different temperatures, thereby producing a temperature gradient across the middle layer for increasing sample processing efficiency (the OA at pages 5-6). The Office concludes that it would have been obvious to one with ordinary skill in the art at the time of the invention to have the heaters comprising the lower heating layer of Zhao be independently set to different temperatures to produce a stable temperature gradient, as taught by Kaltenbach, because a temperature gradient can improve the microfluidic chip by increasing sample processing efficiency.

Applicants respectfully traverse this rejection for the reasons of record and for the additional reasons set forth below.

The obviousness analysis under 35 U.S.C. § 103(a) requires the consideration of the scope and content of the prior art, the level of skill in the relevant art, and the differences between the prior art and the claimed subject matter must be considered. *KSR Int'l Co. v. Teleflex Inc.*, 127 S.Ct. 1727 (2007) (*citing Graham v. John Deere Co.*, 383 U.S. 1, 17 (1966)). To establish a prima facie case of obviousness a three-prong test must be met. First, the prior art must reference must teach or suggest all the claim limitations. *In re Royka*, 490 F.2d 981, 985 (CCPA 1974). Second, there must be some suggestion or motivation, either in the references or in the knowledge generally available among those of ordinary skill in the art, to modify the reference to achieve the claimed invention. *KSR* at 1731. And third, there must be a reasonable expectation of success found in the prior art. *In re Vaeck*, 947 F.2d 488 (Fed. Cir. 1991).

"Rejections on obviousness grounds cannot be sustained by mere conclusory statements." *In re Kahn*, 441 F.3d 977, 987-88 (Fed. Cir. 2007) (citations omitted). Critical elements of the invention as a whole which clearly distinguish the entire invention from the prior art references cannot be ignored. *Panduit Corp. v. Dennison Manufacturing Co.*, 1 U.S.P.Q.2d 1593, 1597 (Fed. Cir.), *cert. denied*, 481 U.S. 1052 (1987). Evidence of an unobvious or unexpected advantageous property can rebut prima facie obviousness. MPEP § 716.02(a). Moreover, if a proposed modification changes the principle of operation of a reference, the teachings of that reference are not sufficient to render the claimed invention obvious. MPEP § 2143.01.VI, *citing In re Ratti*, 270 F.2d 810, 123 USPQ 349 (CCPA 1959).

The relevant teachings of Zhao have been discussed in detail above. Kaltenbach teaches a miniaturized planar column device comprising a thermal controller for regulating temperature, preferably a thermoelectric device comprising Peltier elements (abstract). Kaltenbach further teaches that the thermal controller may be used to provide temperature regulation over the entire surface of the column device, to provide regional temperature regulation, or to provide temperature regulation in such a manner as to generate a temperature gradient along the length of the miniaturized column device (col. 3, line 57 – col. 4, line 3; col. 25, lines 7-49).

Kaltenbach is unable to cure the deficiencies of Zhao since it only teaches a capillary chip for one-dimensional electrophoresis. Kaltenbach does not teach or even suggest a channel layer comprising a plurality of second-dimension microfluidic channels in fluid communication with a first-dimension microfluidic channel, as claimed by the present inventors. On the contrary, every single embodiment disclosed in Kaltenbach describes devices wherein sample separation is achieved by a unidirectional movement of the sample along a microchannel formed between two adjacent planar surfaces by laser ablation or another suitable technique.

It is settled law that if a proposed modification changes the principle of operation of a reference, the teachings of that reference do not render the claimed invention obvious (*In re Ratti*, 270 F.2d 810 (CCPA 1959)). A person skilled in the art at the time of the present invention would have recognized that a two-dimensional or multidimensional electrophoresis is conceptually

different from a one-dimensional electrophoresis in that it permits a much higher level of sample resolution. The difference is not merely quantitative – it is qualitative. As explained in the specification at paragraph **[0015]** and in Figure 7, the presently claimed two-dimensional or multi-dimensional capillary electrophoresis device, combined with a stable thermal gradient, permits separation of two nucleotide molecules of the same size that have as little as one mismatched base pair, thus allowing detection of a nucleotide polymorphism or a single nucleotide polymorphism. None of the devices disclosed in Zhao or Kaltenbach have the same level of resolution, which is the reason why neither reference teaches or even suggests detection of a nucleotide polymorphism or a single nucleotide polymorphism using such one-dimensional electrophoresis devices.

It is also well settled that a prior art reference must be considered in its entirety, i.e., as a whole, including portions that would lead away from the claimed invention. MPEP § 2141.02.VI; *W.L. Gore & Associates, Inc. v. Garlock, Inc.*, 721 F.2d 1540, 220 USPQ 303 (Fed. Cir. 1983), *cert. denied*, 469 U.S. 851 (1984). It is improper to combine references where the references teach away from their combination. MPEP § 2145.X; *In re Grasselli*, 713 F.2d 731, 743, 218 USPQ 769, 779 (Fed. Cir. 1983). Moreover, proceeding contrary to accepted wisdom in the art is evidence of nonobviousness. MPEP § 2145.X; *In re Hedges*, 783 F.2d 1038, 228 USPQ 685 (Fed. Cir. 1986).

As discussed above, the Office cites US 5,599,432, which is incorporated by reference in Zhao, in support of its position that Zhao teaches an upper layer comprising a two-dimensional or multidimensional microfluidic channel. As pointed out above, US 5,599,432 teaches away from the present invention by listing a number of seemingly insurmountable technical difficulties associated with the presently claimed microchannel configuration:

> Coupling a large number of separating capillaries next to one another to achieve "two dimensionality" in order thus to be able also to separate highly complex substance mixtures would, however, require in the case of miniaturised systems connection pieces of subnanolitre volumes. Such connection pieces would, however, be very difficult and expensive to manufacture, if they could be manufactured at all. With very short capillary separating paths for very rapid separations, the disturbing effect of the dead spaces of the connection pieces is particularly high. Those dead spaces would therefore have to be kept

> vanishingly small, which appears to be impossible in practice. The construction of the separating path of a miniaturised capillary electrophoresis system as a flat bed, analogously to 2D gel electrophoresis, would promote the diffusion of the separated components and thus result in a marked impairment of the separating performance. (US 5,599,432 at col. 4, lines 1-17, emphasis added).

The Office should not ignore the fact that Applicants proceeded contrary to the conventional wisdom that two-dimensional capillary electrophoresis was fraught with serious technical challenges in order to arrive at the claimed invention.

In summary, Applicants respectfully submit that neither of the cited references, alone or in combination, teaches or suggests a capillary electrophoresis chip capable of detecting a nucleotide polymorphism or a single nucleotide polymorphism, comprising a plurality of second-dimension microfluidic channels in fluid communication with a first-dimension microfluidic channel. In the absence of a teaching or suggestion of each and every claim element, the cited combination fails to provide the motivation to practice the presently claimed invention. Moreover, by introducing a plurality of second-dimension microfluidic channels in fluid communication with a first-dimension microfluidic channel and by combining an electric gradient with a thermal gradient along the plurality of second-dimension microfluidic channels, the present invention has altered the fundamental principle of operation of the cited references, effectively rebutting the Office's obviousness argument. Additionally, as discussed above, Applicants had to proceed contrary to conventional wisdom in order to arrive at the presently claimed invention, further undermining the obviousness argument. Thus, the Office has failed to establish a *prima facie* case of obviousness, and therefore this rejection under 35 U.S.C. § 103(a) should be withdrawn.

Zhao in View of Kaltenbach, Further in View of Hodes

Claim 4 stands rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Zhao, or alternatively Zhao in view of Kaltenbach, as applied to claim 1 above, and further in view of Hodes (US 3,502,558, hereinafter "Hodes").

The Office alleges that Zhao discloses that the specific design and composition of the driving electrodes on the middle cover layer should be understood by those skilled in the art to be electrically conductive, but does not disclose the specific examples used in electrodes that are electrically conductive. To cure that deficiency of Zhao, the Office cites Hodes, which allegedly discloses a method of depositing gelatin on electrodes made of electrically conductive material such as gold, platinum or graphite. The Office concludes that it would have been obvious to one with ordinary skill in the art at the time of the invention to have the integrated electrodes of the middle layer made of electrically conductive material such as gold, platinum or graphite in the invention of Zhao because Zhao already provides electrodes and as taught by Hodes the suitable electrode material can be any of gold, platinum or graphite because they are electrically conductive (the OA at page 7).

Applicants respectfully traverse this rejection for substantially the same reasons as those set forth above. The relevant teachings of Zhao and Kaltenbach have been discussed in detail above. Hodes merely teaches that gold, platinum or graphite can be used as electrically conductive materials. Much like Zhao and Kaltenbach, Hodes does not teach or even suggest a channel layer comprising a plurality of second-dimension microfluidic channels in fluid communication with a first-dimension microfluidic channel, as presently claimed. As such, Hodes fails to cure the deficiencies of Zhao and Kaltenbach discussed above.

None of the cited references, alone or in combination, teaches or suggests a capillary electrophoresis chip capable of detecting a nucleotide polymorphism or a single nucleotide polymorphism, comprising a plurality of second-dimension microfluidic channels in fluid communication with a first-dimension microfluidic channel. In the absence of a teaching or suggestion of each and every claim element, the cited combination fails to provide the motivation to practice the presently claimed invention. Moreover, by introducing a plurality of second-dimension microfluidic channels in fluid communication with a first-dimension microfluidic channel and by combining an electric gradient with a thermal gradient along the plurality of second-dimension microfluidic channels, the present invention has altered the fundamental principle of operation of the cited references, effectively rebutting the Office's obviousness argument. Additionally, as

discussed above, Applicants had to proceed contrary to conventional wisdom in order to arrive at the presently claimed invention, further undermining the obviousness argument. Thus, the Office has failed to establish a *prima facie* case of obviousness, and therefore this rejection under 35 U.S.C. § 103(a) should be withdrawn.

Zhao in View of Kaltenbach, Further in View of Johnck

Claim 5 stands rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Zhao, or alternatively Zhao in view of Kaltenbach, as applied to claim 1 above, and further in view of Johnck *et al.* (US 2003/0161572, hereinafter "Johnck").

The Office alleges that Zhao discloses that the middle cover layer can be coated with a pressure sensitive adhesive which is then pressed against the substrate containing channels and wells, but does not disclose the specific examples of pressure sensitive adhesives that can be used to coat the middle cover layer. To cure that deficiency of Zhao, the Office cites Johnck, which allegedly discloses a microfluidic analysis system consisting of an upper substrate layer and a middle cover layer with thin-film electrodes integrated thereon, said cover layer coated with polydimethylsiloxane (PDMS) for insulating the exposed electrodes. The Office concludes that it would have been obvious to one with ordinary skill in the art at the time of the invention to have the middle cover layer with integrated electrode components be coated with PDMS in the invention of Zhao because Zhao already provides a coating layer for the cover layer and as taught by Johnck the PDMS coating can electrically insulate the electrodes (the OA at page 8).

Applicants respectfully traverse this rejection for substantially the same reasons as those set forth above. The relevant teachings of Zhao and Kaltenbach have been discussed in detail above. Johnck merely teaches that polydimethylsiloxane (PDMS) can be used for insulating electrodes. Much like Zhao and Kaltenbach, Johnck does not teach or even suggest a channel layer comprising a plurality of second-dimension microfluidic channels in fluid communication with a first-dimension microfluidic channel, as presently claimed. As such, Johnck fails to cure the deficiencies of Zhao and Kaltenbach discussed above.

None of the cited references, alone or in combination, teaches or suggests a capillary electrophoresis chip capable of detecting a nucleotide polymorphism or a single nucleotide polymorphism, comprising a plurality of second-dimension microfluidic channels in fluid communication with a first-dimension microfluidic channel. In the absence of a teaching or suggestion of each and every claim element, the cited combination fails to provide the motivation to practice the presently claimed invention. Moreover, by introducing a plurality of second-dimension microfluidic channels in fluid communication with a first-dimension microfluidic channel and by combining an electric gradient with a thermal gradient along the plurality of second-dimension microfluidic channels, the present invention has altered the fundamental principle of operation of the cited references, effectively rebutting the Office's obviousness argument. Additionally, as discussed above, Applicants had to proceed contrary to conventional wisdom in order to arrive at the presently claimed invention, further undermining the obviousness argument. Thus, the Office has failed to establish a *prima facie* case of obviousness, and therefore this rejection under 35 U.S.C. § 103(a) should be withdrawn.

CONCLUSION

In view of the above, each of the presently pending claims in this application is believed to be in immediate condition for allowance. Accordingly, the Examiner is respectfully requested to withdraw the outstanding rejection of the claims and to pass this application to issue. If it is determined that a telephone conference would expedite the prosecution of this application, the Examiner is invited to telephone the undersigned at the number given below.

In the event the U.S. Patent and Trademark office determines that an extension and/or other relief is required, applicant petitions for any required relief including extensions of time and authorizes the Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 03-1952** referencing **docket No. 514572002400**. However, the Commissioner is not authorized to charge the cost of the issue fee to the Deposit Account.

Dated: November 7, 2008

Respectfully submitted,

Electronic signature: /Yan Leychkis/
Yan Leychkis
Registration No.: 60,440
MORRISON & FOERSTER LLP
12531 High Bluff Drive, Suite 100
San Diego, California 92130-2040
(858) 314-7702